Observed and expected serious adverse event rates in randomised clinical trials for hypertension

Actual and expected serious adverse event rates in randomised clinical trials for hypertension; An observational study comparing trials which do and do not focus on older people

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World count: 3498

Abstract

Introduction

Representativeness of 'standard' antihypertensive drug trials is uncertain, with limited recruitment of older-people. Some trials specifically recruit older participants to address this. If such older-people's trials are representative, we would expect rates of hospitalisation and death in each trial to be similar to community rates, and higher than rates in standard trials.

Methods

We identified trials of Renin-Angiotensin-Aldosterone system (RAAS) drugs for hypertension. Serious Adverse Events (SAEs) are routinely included in trial reports and are predominantly accounted for by all-cause hospitalisations and death. We compared SAE rates in older-people's and standard trials, adjusting for trial characteristics (phase/drug/comparison/outcome). We identified a community cohort of adults with hypertension commencing similar drugs to obtain an expected rate of hospitalisations/deaths, and compared this to observed SAE rates in each trial.

Results

Included 110 trials: 11 older-people's trials exclusively recruited people over 60 years; 99 standard trials included general adult populations (over and under 60-years). Older-people's trials had higher SAEs rate than standard trials (0.18 versus 0.11 events/person/year, adjusted IRR 1.74, 95% CI 1.03-2.92). The hospitalisation and death rate in the community for those taking RAAS antihypertensives was much greater than the rate of SAEs reported in standard (ratio 3.70 (3.12-4.55)) and older-people's trials (4.35 (2.56-7.69)), adjusting for age and sex.

Discussion

Trials report substantially fewer SAEs than expected from rates of hospitalisations and deaths among similar-aged people receiving equivalent treatments in the community. SAE rates may be a useful metric to assess trial representativeness. Clinicians should be cautious when applying trial recommendations to older people, even when trials focus on older participants.

Funding

Wellcome Trust, MRC.

Research in Context

Evidence before this study

We searched Medline from inception to 5th November 2020 without language restriction using terms for "hypertension" and "trials", and ("representative*" or "serious adverse events") for studies assessing representativeness of hypertension trial populations or assessing the rates of SAEs in hypertension trials. Four studies, including 24 different trials, assessed the representativeness of hypertension trials by applying trial exclusion criteria to people with hypertension in routine clinical practice. The proportion of people who were ineligible for trials was between 50% and 100% in most cases. This was true of trials specifically focussing on older adults (e.g. HYVET, SPRINT and OPTiMISE trials) in which polypharmacy, multimorbidity and frailty were associated with ineligibility. This suggests that trial participants are likely to be 'healthier' overall than people treated in the community. Previous studies have not directly compared health-related outcomes of trial participants to real-world populations. Older adults have been shown to have higher rates, and a greater diversity, of adverse events in the trial setting. However, we did not identify any previous studies that systematically assessed rates of SAEs in hypertension trials; that compared SAEs in trials focussing on older people with other trials; or that compared SAEs in the trial population to similar events in community populations.

What this study adds

After systematically identifying hypertension trials of drugs acting on the renin-angiotensin-aldosterone system, we demonstrated that trials focussing on older people had a significantly higher rate of SAEs than comparator 'standard' trials which did not focus specifically on older people. As would be expected, this suggests that trials focussing on older people recruited people with a greater risk of adverse health outcomes than trials including all ages. However, the rate of all-cause hospitalisations and deaths (which, by definition, would be SAEs in trial populations) among people with hypertension treated in the community was on average four-times higher than the SAE rate in

the trials, after adjusting for age and sex. This difference was similar for standard trials and trials focusing on older people. Therefore, despite having a higher risk of SAEs than in standard trials, people included in hypertension trials focused on older people have a considerably lower incidence of adverse health outcomes than people of a similar age, receiving similar treatment in the community. This demonstrates that there are clinically meaningful differences between trial populations and people treated for hypertension in the community. Furthermore, where SAE rates in trials are lower than expected, this should prompt careful consideration of trial exclusion criteria and population characteristics when assessing representativeness and applicability.

Implications of all the available evidence

Our findings demonstrate that people in hypertension trials experience substantially lower rates of adverse health outcomes than people with hypertension treated with similar drugs in the community. This adds weight to the body of evidence showing that hypertension trials are under-representative of their target populations. However, our findings also add nuance to this statement, as trials focussing on older people do have a significantly higher rate of SAEs than standard trials. Therefore, trials focussing on older people do, at least in part, reflect the increased risk of adverse outcomes seen in older populations. Trials focussing on older people therefore have an important role in informing treatment decisions in older people, but should be viewed with caution as, like standard trials, they are not representative of community populations. Our findings also indicate that SAE rates should be considered as a novel metric with which to assess the representativeness of trial populations, through comparison with the incidence of similar events in routine clinical care. Such an approach could facilitate more direct quantification of the consequences of trial under-representativeness, however this would require consistent and complete recording and reporting of SAEs as well as reliable estimates of event rates in the community.

Introduction

Hypertension is a common and important modifiable risk factor for major cardiovascular disease. Hypertension is associated with age, with over 75% of people over 80 years old diagnosed with hypertension.[1] There is uncertainty, however, about how hypertension should best be managed in older people.[2] The risk of cardiovascular disease associated with hypertension may reduce as people age,[3] particularly in the context of frailty.[4] Furthermore, antihypertensive treatment presents a range of potential risks which may disproportionately impact older people.

Whilst randomised controlled trials provide the least biased estimates of treatment efficacy, there are concerns that trial participants are often not representative of people treated for hypertension in routine clinical practice.[5] Specifically, older people are often excluded from trials.[6] This can occur directly, through age-based exclusion criteria, or indirectly through other exclusion criteria (e.g. comorbidity or co-prescribing) as well as the trial recruitment process.[6,7] To address this problem and provide evidence to guide treatments of older people, some trials have focussed explicitly on older people.[8,9] However, such trials often only enrol a fraction of those invited to participate.[10] Consequently, it remains unclear whether conducting trials specifically among older people is sufficient to overcome the difficulties in applying trial evidence to older people encountered in routine clinical practice.

Older people have a greater risk of adverse health outcomes in routine care settings, and in trials.[11] This is likely to be driven by characteristics such as frailty, multimorbidity (increasing the risk of drug-disease interactions) and polypharmacy (increasing risk of drug-drug interactions), and decreased kidney and liver function. All are more common in older age, associated with poor health outcomes, and often under-represented within trials.[12-16]

Previous studies assessing trial representativeness have tended to apply trial exclusion criteria to population samples derived from routine healthcare data or disease registries, concluding that many people living with long-term conditions would be ineligible for trials.[5,6,10,17] However, such an

approach does not directly assess the health outcomes in trial participants compared to those receiving routine care. One potential alternative approach is to analyse Serious Adverse Events (SAEs). SAEs in a trial setting are events which are either life threatening, lead to death, cause or prolong hospitalisation, result in serious or lasting impairment or disability, or cause a birth defect. Regulatory bodies require that trial sponsors record and report all SAEs,[18] while recording SAEs is also part of the CONSORT statement for the publication of trial findings.[19] Importantly, SAEs are required to be reported irrespective of the suspected cause, as well as for both treatment and control arms. Therefore, SAEs should provide a reliable measure of the rate of adverse health outcomes (particularly resulting in hospitalisation and death) within a trial population. Indeed, if a trial was perfectly representative, we would expect the SAE rate of that trial to be similar to hospitalisation and death rates among the "target" patients with the same condition to which we would hope to apply the trial results. We would also expect trials involving older people to have higher SAE rates than trials for the same indication recruiting a more general adult population.

The aim of this paper is to compare the rates of SAEs in trials of older people with the rates in trials not focussing specifically on older people ('standard trials') and compare these findings to the rate of SAEs (i.e. rate of hospitalisation and death) in people with hypertension starting a similar treatment in routine clinical practice, adjusting for age and sex. As an exemplar, here we focus on drugs to treat hypertension acting on the renin-angiotensin-aldosterone system (RAAS). RAAS drugs were chosen as they are commonly used to treat hypertension, including in older people. There are also concerns that older people are under-represented in RAAS trials.[5,17,20] Furthermore, associated risks such as renal dysfunction, orthostatic hypotension, syncope, and polypharmacy are likely to be greater in older people.[21]

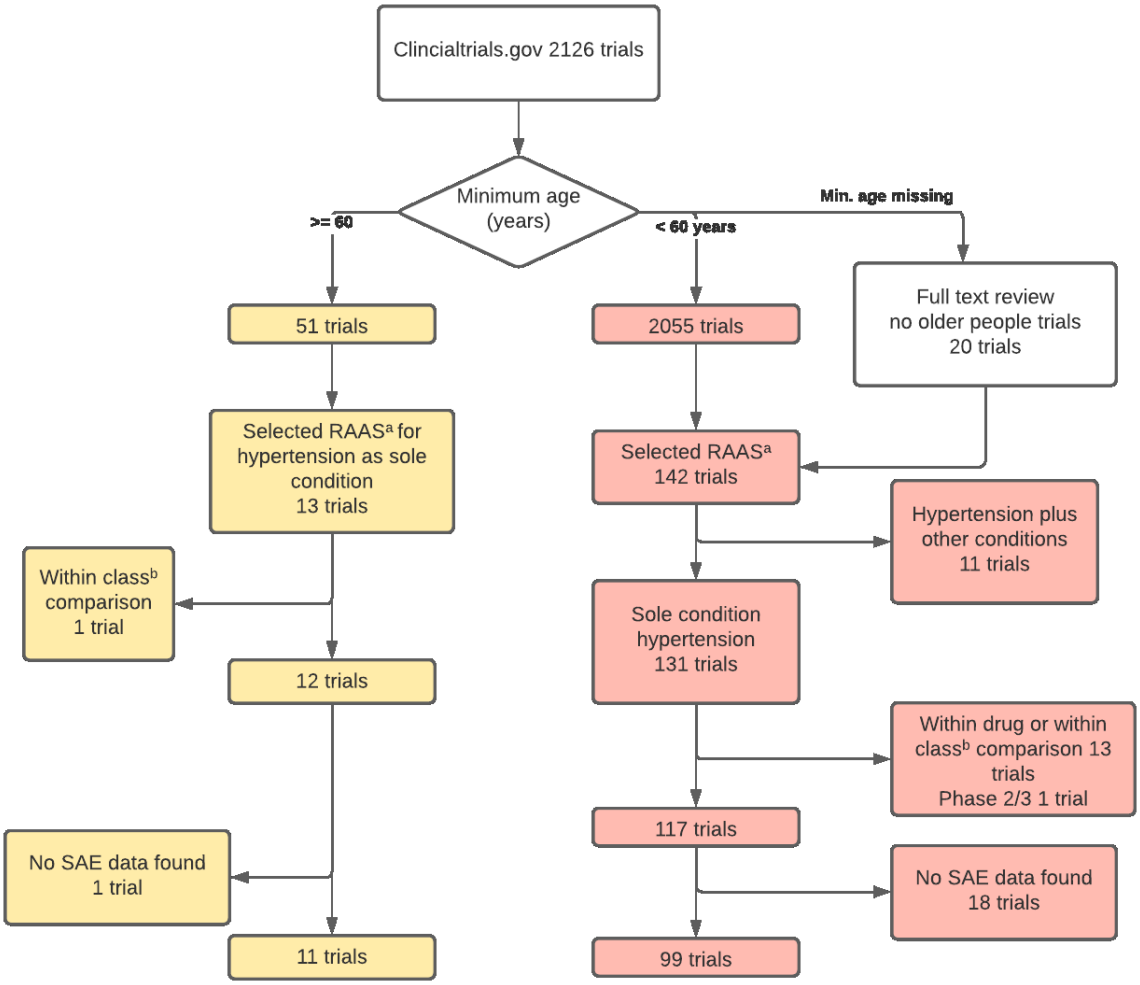
Methods

This study compares SAE rates in registered randomised controlled trials of RAAS drugs to treat hypertension with a community sample of people with hypertension who were initiated on RAAS drugs

Study design and participants

Trials were identified from an extract on 1st August 2017 of all clinical trials registered at clinicaltrials.gov (a registry of clinical trials from across the world managed by the United States National Institutes of Health), to which we had applied World Health Organisation Anatomic Therapeutic Chemical (WHO ATC) drug classes for all interventions.[12] To be eligible, trials had to be registered from 1999 onwards, be phase 2-3, 3, or 4, have eligibility criteria published in English, and be evaluating RAAS drugs for the treatment of hypertension. We included trials in two stages (Figure 1). First, we identified all trials with a minimum inclusion age of 60-years or older and defined these as trials of older people. We reviewed these to identify drugs and indications for which such trials were commonly undertaken. Secondly, we obtained, as a comparator group, all 'standard' trials for the same indications and drugs with a minimum inclusion age <60 years. We included trials undertaken in any country, single- or multi-centre trials, with published or unpublished results.

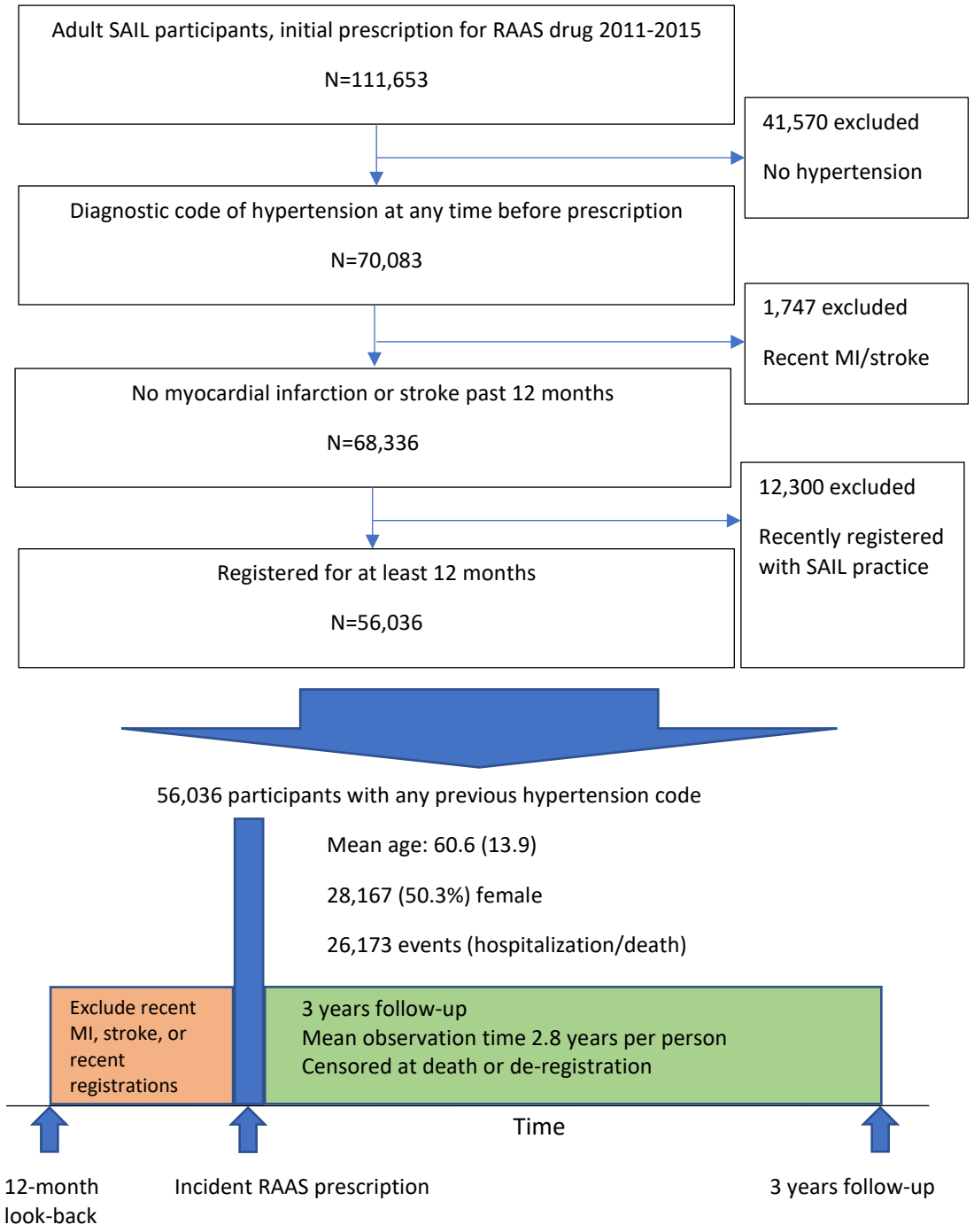
Figure 1:



Legend: "Missing" refers to the fact that the entry for the specific field in clincialtrials.gov for the minimum age was missing. The full text of the trial registration was then reviewed to identify if the trial was targeted specifically at older participants. a) All RAAS drugs were permitted for the selection of eligible older people trials. Only trials which were studied in one or more of the older person trials (aliskiren, irbesartan, olmesartan, telmisartan or valsartan) were selected for the comparator group of the standard trials. b) Within drug comparisons refers to trials where all arms included the same drug (eg trials of different dosages or regimens). Between class comparisons refers to trials where all arms included drugs with the same 5-character ATC class (eg drugs in WHO ATC class C09CA are all angiotensin II receptor blockers).

The community comparison sample was identified using the Secure Anonymised Information Linkage (SAIL) databank. SAIL collects routine healthcare data (including primary care diagnostic codes and prescriptions, with linked hospital and mortality data) from participating practices in Wales, UK (covering approximately 70% of the Welsh population). SAIL participants are representative of the Welsh population in terms of age, sex and socioeconomic status. We identified participants with a previous diagnostic code for hypertension in primary care who were prescribed a RAAS drug for the first time. We excluded participants who registered with a SAIL practice less than 12 months before starting the RAAS drug. We also excluded people with any coded myocardial infarction or stroke occurring in the 12 months prior to initiation (as these people were unlikely to be receiving the RAAS drug solely to treat hypertension, so are likely to have higher rates of hospitalisation and death). Figure 2 summarises participant selection and exclusions. As a sensitivity analysis, we also excluded all SAIL participants with a previous code for diabetes mellitus, chronic kidney disease, or heart failure.

204 Figure 2: Inclusion and analysis of SAIL participants for community comparison



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Measures

For the trials we extracted the following information from clinicaltrials.gov, clinical trial reports and published papers (all data on https://github.com/dmcalli2/adverse_events_older_people): baseline characteristics of the trial participants (age, sex, body mass index), number of trial participants, trial phase, trial drug, comparison treatment, outcomes, follow up times, and the occurrence of serious adverse events (total number of events). SAE reporting is a regulatory requirement for trials,[18] with SAEs defined as any event which is life threatening, leads to hospitalisation or death, results in serious or lasting impairment or disability, or causes a birth defect.[22] Among these, hospitalisations and deaths are the most common. We also recorded whether the trial outcome was a hard outcome (i.e. a clinical endpoint such as major adverse cardiovascular event or mortality), or soft outcome (i.e. a surrogate marker such as change in blood pressure). For trials with hard outcomes, the number of clinical endpoint events was added to the number of SAEs before comparing event rates to the community population (as both endpoint and SAEs are likely to represent hospitalisation or deaths). We included SAEs and clinical endpoints from both the treatment and control arms of each trial, as most SAEs in the trial setting are not specifically related to the trial treatment.[23] To confirm this, we also compared SAE rates in the treatment and placebo arms.

For each participant in the community sample we identified age and sex. We then calculated the number of emergency/urgent hospitalisations (excluding elective admissions) or deaths occurring over 3 years follow-up. Participants were censored at death or if they de-registered from a participating practice within the 3-year period.

Statistical analyses

Our first analysis compared the SAE rate in trials of older people with standard trials, adjusting for trial characteristics. We modelled SAEs on older people trial status using hierarchical Poisson regression models (random intercept, Poisson likelihood); unadjusted (offset by estimated person time (calculated as follow-up * (number of participants - 0.5 * number of SAEs))) and adjusting for

direct renin inhibitor trial (yes/no), comparison type (placebo, different ATC class to 3-character, different ATC class to 5-character), phase (3 or 4) and outcome type (hard or soft). The adjusted model was the pre-specified primary analysis. Models were fitted using Rstanarm to allow fitting of the random intercept for the trials.

We also used Poisson regression to model the age and sex specific rate of unplanned hospital admission or death in the 3 years following initiation of RAAS drugs in SAIL. This model fitted the data well (appendix p 1-4) and the covariates and variance covariance matrix were exported from the SAIL secure platform to allow us to calculate the expected number of hospitalisations and deaths for each trial population. Having calculated the expected rate of hospitalisations and deaths (as a proxy for SAEs), we calculated the ratio of expected to observed SAEs. We used the truncated normal distribution to estimate the age distribution for each trial based on the reported mean age as well as any age cut-offs used as exclusion criteria. In a previous analysis of trial IPD (including trials with the same eligibility criteria as those in this sample) the truncated normal distribution was found to accurately represent the age distribution of trials in this context.[12] We obtained uncertainty intervals for the observed/expected ratio for each trial as follows. We obtained 10,000 samples of the intercept, age and sex coefficients by sampling from a multivariate normal distribution where the parameters were the point estimates and variance covariance matrix for the SAIL Poisson regression models. For each sample we applied the coefficients to the age-sex distribution of each trial to obtain 10,000 samples from the distribution of the expected count. We then divided each of these by each of 10,000 samples from a Poisson distribution (where the parameter was the observed count) to obtain 10,000 samples representing the uncertainty distribution for the observed/expected ratio, which we summarised by the mean, 2.5^{th} and 97.5^{th} centiles.

We obtained the standardised ratio of hospitalisations and deaths in the community and SAEs in the trials by treating the log of the expected count (which was obtained by applying the SAIL-derived age-sex specific rates to the age-sex distribution of each trial) as an offset term in the regression

model (hierarchical Poisson regression model as described above). The first model compared standard and older people trials. The second further adjusted for trial characteristics.

We performed three sets of sensitivity analyses. First, in view of the small number of older people trials, we re-ran the regression models having excluded each trial in turn to examine the sensitivity of the findings to trial characteristics. The second sensitivity analysis explored the impact of possible misclassification of the indication for RAAS treatment within the community cohort. For this, in addition to excluding participants with recent myocardial infarction or stroke (as in the main analysis), we also excluded any participant with a previous diagnosis of diabetes mellitus, heart failure, or chronic kidney disease. We then repeated all analyses comparing trials to the community cohort. Finally, as the trial follow-up periods were shorter than the observation time of the community cohort, we repeated all analyses limiting follow-up of the community sample to the first 90 days following initial prescription (to mirror the median follow-up in the older people's trials) and analysing first event only (i.e. censoring at 90 days, first hospitalisation or death, whichever happened first).

All analyses were performed using R version 3.6.1. The full analysis code and all data are available at github repository https://github.com/dmcalli2/adverse_events_older_people.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data. DM had the final responsibility to submit for publication.

Results

We included 110 trials, of which 11 (10%) were trials in older people and 99 (90%) were standard trials which did not focus specifically on older people. Trial details are summarised in table 1. The median number of SAEs per trial was 7.5 (interquartile range [IQR] 3-14). The median rate of SAEs per person per year was 0.18 (IQR 0.12-0.29) in the older people trials and 0.11 (0.08-0.18) in the standard trials. These SAE rates refer to the whole trial population, as among the placebo-controlled trials SAE rates were similar between treatment and control arms.

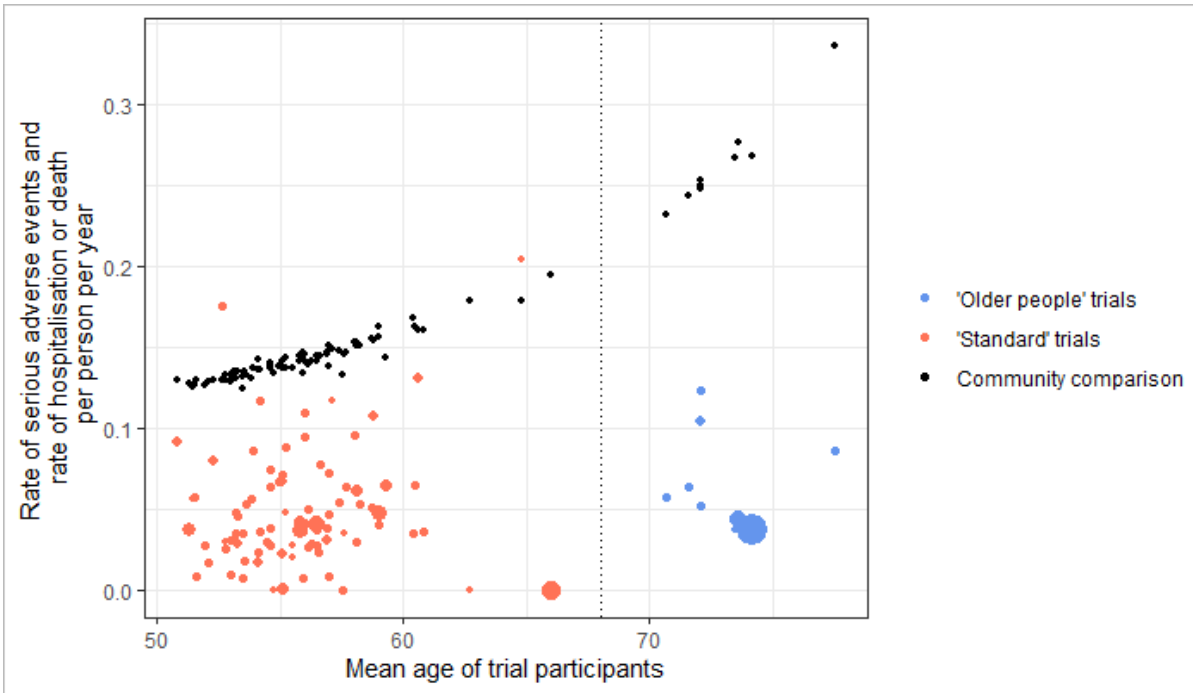
Table 1: Summary of included trials

	Standard trials (n = 99)	Older-people trials (n = 11)	Community
Mean age	Median of trial mean ages: 55.6 (IQR 53.7 to 57.0)	Median of trial mean ages: 73.1 (IQR 71.6 to 74.2)	60.6 (sd 13.9)
% women	Median 45% (IQR 40% to 49%)	Median 55% (IQR 52% to 55%)	50.3%
Drug under investigation Angiotensin receptor blocker Renin inhibitor	 66 (67%) 33 (33%)	 8 (73%) 3 (27%)	-
Comparison Placebo Drug of different class	 22 (22%) 77 (78%)	 1 (9%) 10 (91%)	-
Phase 3 4	 67 (68%) 32 (32%)	 5 (46%) 6 (54%)	-
Trial endpoint Hard Soft	 1 (1%) 98 (99%)	 2 (18%) 9 (82%)	-
Trial sample size	Median 722 (474 to 1124)	Median 754 (388 to 884)	-
Trial follow-up (days)	Median 63 (56 to 98)	Median 98 (56 to 252)	-
Footnote: Data for each trial are available at https://github.com/dmcalli2/adverse_events_older_people including data on baseline blood pressure (4/11 older people's trials and 46/99 standard trials), comorbidity status (3/11 older people's trials and 37/99 standard trials), and ethnicity (2/11 older people's trials and 39/99 standard trials). These are not summarised above due to the high proportion of missing data.			

Before adjusting for trial characteristics, the incident rate ratio (95% credible interval) for older versus standard trials was 1.57 (0.95 to 2.57). After adjusting for trial characteristics including trial drug, type of comparison, trial phase and type of outcome, older-people trials had a higher incidence of SAEs (IRR 1.74, 95% credible interval 1.03-2.92) than did standard trials.

The expected age- and sex-adjusted rates of all-cause hospitalisation and death among people with hypertension starting RAAS drugs in routine clinical practice is shown on figure 3. Coloured points show the observed rate of SAEs in each trial, while the black points show the expected SAE rate obtained by applying community all-cause hospitalisation and death rates to the age and sex distribution of each trial (each coloured point has a black point which is its pair, but lines connecting these are not shown for clarity). The observed rates were consistently lower than the expected rates (shown by the coloured points in figure 3).

Figure 3: Observed versus expected SAEs per trial



Legend: The observed rate of SAE per trial is shown by the coloured points (red = standard, blue = older people). Points are plotted at the mean age for the trial. The expected number of hospitalisations and deaths for each trial, based on the age/sex specific rates from SAIL applied to the age/sex distribution of the trial, is shown by the black points. Trial sample size for trials is indicated by the size of the coloured points.

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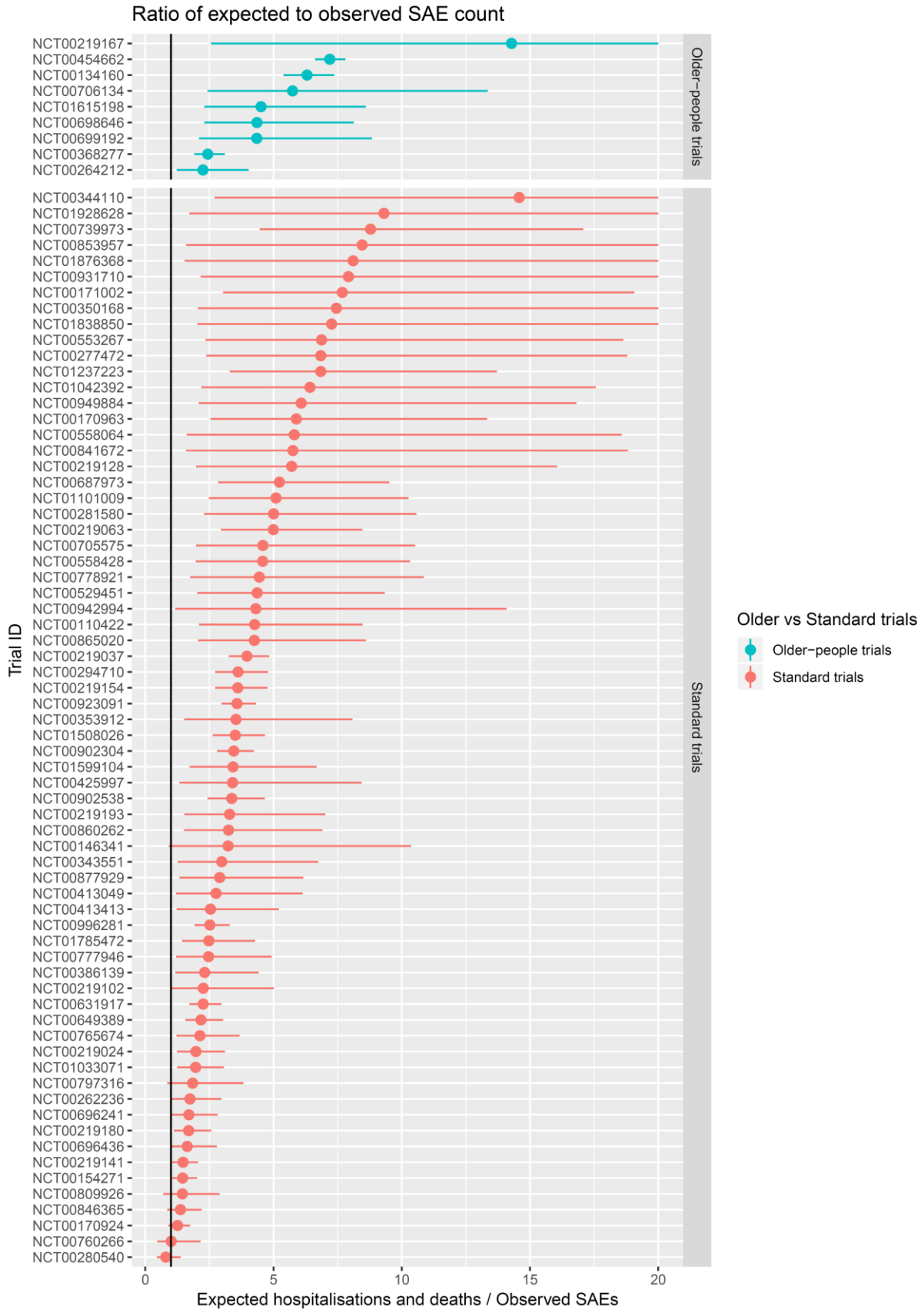
297 A formal comparison of the ratio between the observed SAE rate and the expected rate of
298 hospitalisation and death for each trial (adjusted for age and sex) is shown in figure 4. For all but one
299 of the trials, the rate of SAEs was lower than the expected rate of hospitalisation and deaths given
300 the age/sex distribution of trial participants. There was considerable heterogeneity in the calculated
301 ratios, both within the older people's trials and the standard trials. However, across all trials, the
302 reported rate of SAEs was considerably lower than would be expected to occur if the trials were
303 representative of people with hypertension taking RAAS drugs in the community. The standardised
304 ratio (SR) was 3.70 (95% CI 3.12-4.55) for 'standard trials' and 4.35 (95% CI 2.56-7.69) for 'older
305 people trials', indicating that hospitalisations and deaths occurred more than four times more
306 frequently among people taking RAAS drugs in the community than SAEs occurred in trials. The
307 magnitude of risk increase for SAEs in community patients taking RAAS did not differ, when
308 comparing standard and older people trials (ratio of SR 1.16; 95% CI 0.67-2.04). The results were

similar after adjusting for agent, type of outcome (clinical endpoint yes/no), type of comparison and phase (adjusted SR 4.00; 95% CI 2.50-6.25 for standard trials, 4.55; 95% CI 2.08-10.00 for older people's trials, and ratio of SRs 1.11; 95%CI 0.59-2.04).

In the first sensitivity analysis, the effect estimates were similar on leaving out each trial in turn. In the second sensitivity analysis, the difference between trials and the community was similar after further excluding people with diabetes mellitus, heart failure or chronic kidney disease from the community sample, to minimise the risk of misclassification of the indication for RAAS treatment (see appendix p 5-7). In the final sensitivity analysis, limiting the community follow-up to 90 days to mirror that of the trials, the difference between trials and community was also similar (see appendix p 8-10).

Figure 4


Ratio of expected to observed SAE count
Trial ID
NCT00219167
NCT00454662
NCT00134160
NCT00706134
NCT01615198
NCT00698646
NCT00699192
NCT00368277
NCT00264212
Older−people trials
NCT00344110
NCT01928628
NCT00739973
NCT00853957
NCT01876368
NCT00931710
NCT00171002
NCT00350168
NCT01838850
NCT00553267
NCT00277472
NCT01237223
NCT01042392
NCT00949884
NCT00170963
NCT00558064
NCT00841672
NCT00219128
NCT00687973
NCT01101009
NCT00281580
NCT00219063
NCT00705575
NCT00558428
NCT00778921
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NCT00110422
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NCT01508026
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NCT00996281
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NCT00777946
NCT00386139
NCT00219102
NCT00631917
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NCT00765674
NCT00219024
NCT01033071
NCT00797316
NCT00262236
NCT00696241
NCT00219180
NCT00696436
NCT00219141
NCT00154271
NCT00809926
NCT00846365
NCT00170924
NCT00760266
NCT00280540
Standard trials
0
5
10
15
20
Expected hospitalisations and deaths / Observed SAEs
Older vs Standard trials
Older−people trials
Standard trials

Figure 4 legend: Each point (with 95% confidence intervals) shows the ratio of expected all-cause hospitalisations or deaths (given the estimated age/sex distribution of each trial) to the observed SAE count in each trial. Four trials reported no SAEs and the ratio was therefore infinite, and are excluded from this plot. The plot also excludes a further 7 trials with only one reported SAE and ratios >50.

Discussion

In this analysis of trials of RAAS drugs for hypertension, trials specifically recruiting older people (all >60 years, mean age >70) had a significantly higher incidence of SAEs than standard trials after adjusting for trial characteristics. This suggests that trials of older people do recruit participants with a higher baseline risk of adverse health outcomes.

Nonetheless, in both trials of older people and standard trials, the rate of SAEs was substantially lower than expected based on the incidence of hospitalisation and death (which would be classed as SAEs in all trials) in people with hypertension being treated in the community. The difference was large, with rates of hospitalisations and death in the community on average four times greater than the rate of SAEs in the trials. This suggests that, even accounting for age and sex, participants in hypertension trials and people with hypertension in the community are very different populations. These differences may reflect differences in the study setting (although hospitalisation rates in the UK are comparable with other OECD countries) as well as demographic and clinical differences in the included populations. These differences may include comorbidity and underlying health status (with differences driven in part by trial exclusion criteria) as well as other factors such as ethnicity, socioeconomic status, hypertension severity, healthcare utilisation and medication adherence. Of note, many of these factors were not reported in the included trials.

This difference between trial and community populations was similar for older-people trials and for standard trials. This does not necessarily mean trial findings are inapplicable. Relative treatment benefits estimated in trials will often be applicable even where there are differences between trial and target populations,[24] but net benefit may still vary because adverse events are more common, and optimal choice of drug may be affected by comorbidity and co-prescribing. This suggests that clinical guideline developers are correct to be cautious when applying trial evidence to community populations. This is particularly true for older, multimorbid or frailer populations, and remains true even when trials are deliberately targeted at older people.

While these findings suggest that trials are under-representative in terms of underlying risk of adverse health outcomes, there are two alternative explanations which could also contribute to the difference between trials and the community sample. First, trials may under-report the true incidence of SAEs. Despite reporting guidelines,[19] there is inconsistency in how SAEs are reported.[25] On the other hand, trial recorded SAEs include other events meaning that trial SAE incidence would be expected to be higher than the community events examined. Second, our community sample may include people taking RAAS for other indications, for whom the risk of hospitalisations and deaths may be higher. For this reason, the primary analysis excluded people with recent myocardial infarction or stroke, and sensitivity analysis excluded people with a history of diabetes, chronic kidney disease, or heart failure, with consistent findings across all analyses. Nonetheless, we cannot be certain about the true indication for starting RAAS drugs from routine data alone. Both underreporting of SAEs and misclassification of the community comparison may bias our estimation of the difference between trials and community samples in the direction that we observed. However, the difference between trials and community populations was large (median 4-times higher rate in the community than in trials) and it is likely that the observed lower rates of SAEs in trial populations is true.

Our findings have implications for interpreting trials that specifically recruit older people. On one hand, trials focusing on older people are likely to be helpful in informing treatment decisions as they successfully recruit older people at a higher risk of serious adverse events than standard trials, thus capturing some of the increased risk experienced. However, concerns about trial representativeness are still well founded, as suggested by the difference between SAEs and hospitalisation and death rates in the community. We observed that the difference between trials and community event rates were similar in both trials of older people and standard trials, suggesting they were similarly under-representative. This suggests that trials focussing on older people present only part of the solution to informing treatment decisions in older people, particularly those at higher risk of adverse health outcomes, such as people living with frailty.

The higher rate of hospitalisations and deaths in the community population has some important implications for managing hypertension in older people. First this finding is likely to reflect a higher prevalence and severity of frailty in community populations compared to trials, which may modify the relationship between hypertension and cardiovascular risk.[4] We previously showed, in an individual-level participant data analysis, that frailty is associated with SAEs in trials.[13] Furthermore, frailty in participants in cardiovascular trials is associated with adverse cardiovascular outcomes independently of traditional risk factors.[26] While frailty has been shown to be present in trials for hypertension in older people,[8,9] frailty in these trials is thought to be less severe than in the community.[2] People living with severe frailty are likely to be excluded from clinical trials, however such individuals are commonly prescribed these medications in the community, often in the context of polypharmacy. The applicability of trial evidence, even those recruiting older people, needs careful consideration when applied to a broader population. It is also likely that such evidence is insufficient to inform treatment decisions in some patient groups, such as people living with severe frailty.

Second, the difference in SAEs between trial and community populations may impact the net benefit of treatment when used in routine clinical practice.[27] For example, higher competing mortality risks in the community may mean that benefits in terms of absolute treatment effects (based on trial participants) are overestimated.[28] Also, if drug-related SAEs were more common in the community (for example, among people living with frailty) this may reduce the net benefit of treatment.[29,30] For example, even if drugs reduce cardiovascular outcomes, net benefit may get smaller if SAE rates increase rapidly with age. Quantifying net benefit would require analysis of differential treatment effectiveness and also treatment-related SAEs, neither of which are possible with this data. However, our findings do indicate that clinicians and guideline developers should be cautious when applying trial estimates of benefit to the wider population.

Strengths of this study include a systematic identification of registered trials. By searching using a trial register and hand-searching clinical study reports we were able to include both published and unpublished trials, limiting publication bias. Limiting our search to clincaltrials.gov may have resulted in a small proportion of studies not being included in our investigation. However, clinicaltrials.gov is the largest international trial registry and trial pre-registration is required both for publication in high-impact journals and to qualify as evidence for regulatory agencies such as the United States Food and Drug Administration.[18] Moreover, it provided a single sampling frame from which we could draw all older people and standard trials. Limiting our search to trials started after 1999 ensured that trials were conducted in a similar time-period to the community comparison, and is a period in which trial registration is increasingly commonplace, however this will have led to the exclusion of earlier trials, including of commonly-prescribed RAAS drugs such as angiotensin-converting enzyme inhibitors. The systematic comparison of SAE rates with hospitalisation and death rates in the community for people with hypertension is novel and builds upon previous studies of trial representativeness by comparing actual health-related outcomes rather than inclusion criteria. Nonetheless, comparing SAEs to hospitalisations and deaths is not an exact like-for-like comparison. SAEs have a broader definition which includes events perceived to be life threatening as well as events leading to impairment or disability (which may not necessarily result in hospitalisation). However, hospitalisations and deaths are, by definition, SAEs and so any bias is very likely towards under-estimating the difference between trial and community rates. Trial data were reported inconsistently, and for some trials we had to estimate the observation time in the trial (based on follow-up length and the SAE rate). Also, as we have highlighted above, we were not able to verify the indication for RAAS drugs in the community. While we excluded participants with recent events which would be alternative indications, there may be some participants prescribed RAAS drugs for reasons other than hypertension. This study focussed on RAAS drugs for hypertension, and the findings may not necessarily be generalisable to other drugs or indications, particularly as SAE rates for angiotensin-receptor blockers may be lower than for other antihypertensives.[29]

Conclusion

Our study shows that participants in hypertension trials experience substantially lower rates of serious adverse health outcomes than people with hypertension treated with similar drugs in the community. Our work suggests assessment of the rate of SAEs, when compared to the expected rate from representative “target” populations, may be a useful metric of trial representativeness. Our findings also show that the problem of under-representativeness is not resolved by recruiting older people to trials, as both older people trials and standard trials were also under-representative in terms of SAEs. This observation emphasises the need for developing approaches to design and execution which enable older people living with frailty to become trial participants.

Authors contributions

JR, AS and DM conceived the study. JR, NC, GR, PH and DM extracted the data from trials. PH and DM acquired and processed the data from SAIL. PH and DM conducted the statistical analysis. All authors were involved in interpretation of the findings. PH and JR wrote the first draft. All authors reviewed the manuscript and made critical changes for intellectual content. All authors read and approved the final manuscript.

Conflict of interest statements

None to declare

Role of funding source

PH is funded through a Clinical Research Training Fellowship from the Medical Research Council (Grant reference: MR/S021949/1). DM is funded via an Intermediate Clinical Fellowship and Beit Fellowship from the Wellcome Trust ("Treatment effectiveness in multimorbidity: Combining efficacy estimates from clinical trials with the natural history obtained from large routine healthcare databases to determine net overall treatment Benefits." - 201492/Z/16/Z). None of the funders had any influence over the study design, analysis or decision to submit for publication.

Ethics committee approval

Not applicable

Data sharing statement

All trial data and analysis code is available at https://github.com/dmcalli2/adverse_events_older_people. Aggregate data from SAIL, along with all model parameters, are available at the same Github address and summarised in the online appendix p 1-4.

References

1. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *Jama* 2005; **294**(4): 466-72.
2. Russo G, Liguori I, Aran L, et al. Impact of SPRINT results on hypertension guidelines: implications for "frail" elderly patients. *J Hum Hypertens* 2018; **32**(8): 633-8.
3. Lewington S. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903-13.
4. Todd OM, Wilkinson C, Hale M, et al. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. *Age and Ageing* 2019; **48**(5): 627-35.
5. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? *The Annals of Family Medicine* 2006; **4**(2): 104-8.
6. He J, Morales DR, Guthrie B. Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. *Trials* 2020; **21**(1): 1-11.
7. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. *Journal of clinical epidemiology* 1999; **52**(12): 1143-56.
8. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine* 2008; **358**(18): 1887-98.
9. Wright Jr JT, Whelton PK, Reboussin DM. A randomized trial of intensive versus standard blood-pressure control. *The New England journal of medicine* 2016; **374**(23): 2294.
10. Sheppard JP, Lown M, Burt J, et al. Generalizability of blood pressure lowering trials to older patients: cross-sectional analysis. *Journal of the American Geriatrics Society* 2020.
11. Luo J, Eldredge C, Cho CC, Cisler RA. Population analysis of adverse events in different age groups using big clinical trials data. *JMIR medical informatics* 2016; **4**(4): e30.
12. Hanlon P, Hannigan L, Rodriguez-Perez J, et al. Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: an individual-level participant data analysis. *BMC Med* 2019; **17**(1): 201.
13. Hanlon P, Butterly E, Lewsey J, Siebert S, Mair FS, McAllister DA. Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. *BMC Med* 2020; **18**(1): 1-12.
14. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. *Journal of the American Society of Nephrology* 1993; **3**(7): 1371-7.
15. Davies E, O'mahony M. Adverse drug reactions in special populations–the elderly. *Br J Clin Pharmacol* 2015; **80**(4): 796-807.
16. Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* 1989; **9**(2): 297-301.
17. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *Jama* 2007; **297**(11): 1233-40.
18. US Food and Drug Administration Authority. Guidance for Industry and Investigators: Safety reporting requirements for INDs and BA/BE studies. 2012. https://www.fda.gov/files/drugs/published/Safety-Reporting-Requirements-for-INDs-%28Investigational-New-Drug-Applications%29-and-BA-BE-%28Bioavailability-Bioequivalence%29-Studies.pdf. Accessed March 2021
19. Ioannidis JP, Evans SJ, Gøtzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of internal medicine* 2004; **141**(10): 781-8.

20. Konrat C, Boutron I, Trinquart L, Auleley G-R, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. *PloS one* 2012; **7**(3): e33559.
21. Albasri A, Hattle M, Koshiaris C, et al. Association between antihypertensive treatment and adverse events: systematic review and meta-analysis. *bmj* 2021; **372**.
22. US Food and Drug Administration Authority. What is a serious adverse event? . https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event Accessed June 2021
23. Mahr A, Golmard C, Pham E, Iordache L, Deville L, Faure P. Types, frequencies, and burden of nonspecific adverse events of drugs: Analysis of randomized placebo-controlled clinical trials. *Pharmacoepidemiology and drug safety* 2017; **26**(7): 731-41.
24. National Institute for Health and Care Excellence. Evidence Synthesis TSD series. 2011. http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/. Accessed June 2021
25. Phillips R, Hazell L, Sauzet O, Cornelius V. Analysis and reporting of adverse events in randomised controlled trials: a review. *BMJ open* 2019; **9**(2): e024537.
26. Farooqi MA, Gerstein H, Yusuf S, Leong DP. Accumulation of Deficits as a Key Risk Factor for Cardiovascular Morbidity and Mortality: A Pooled Analysis of 154 000 Individuals. *Journal of the American Heart Association* 2020; **9**(3): e014686.
27. Dahabreh IJ, Hayward R, Kent DM. Using group data to treat individuals: understanding heterogeneous treatment effects in the age of precision medicine and patient-centred evidence. *International journal of epidemiology* 2016; **45**(6): 2184-93.
28. Welch HG, Albertsen PC, Nease RF, Bubolz TA, Wasson JH. Estimating treatment benefits for the elderly: the effect of competing risks. *Annals of internal medicine* 1996; **124**(6): 577-84.
29. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs meta-analyses of randomized trials. *Journal of hypertension* 2016; **34**(10): 1921-32.
30. Hanlon JT, Pieper CF, Hajjar ER, et al. Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2006; **61**(5): 511-5.